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Zeichen des Anmelders / Vertreter - Applicant / Representative ref. no. - Référence du demandeur ou du mandataire
H100208WO/brä ✓

Anmelder / Applicant / Demandeur : **Honeywell Specialty Chem. ...** Datum / Date **28.05.04**

Empfangsbescheinigung / Receipt for documents / Récépissé de documents

Das Europäische Patentamt bescheinigt hiermit den Empfang folgender Dokumente:
The European Patent Office hereby acknowledges the receipt of the following:
L'Office européen des brevets accuse réception des documents indiqués ci-dessous:

A. **Internationale** Anmeldung / **International** application / Demande **internationale**

Stückzahl / No.of copies / Nombre d'exemplaires

- ☒ Antrag / Request / Requête — 1
- ☒ Beschreibung (ohne Sequenzprotokollteil) / Description (excluding sequence listing part) / Description (sauf partie réservée au listage des séquences) — 3
- ☒ Patentansprüche / Claim(s) / Revendication(s) — 3
- ☒ Zusammenfassung / Abstract / Abrégé — 3
- ☐ Zeichnung(en) / Drawing(s) / Dessin(s) —
- ☐ Sequenzprotokollteil der Beschreibung / Sequence listing part of description / Partie de la description réservée au listage des séquences —
- ☐ Diskette / Disquette —
- ☐ Kopie der allgemeinen Vollmacht / Copy of general power of attorney / Copie du pouvoir général —
- ☐ Prioritätsbeleg(e) / Priority document(s) / Document(s) de priorité —
- ☒ Blatt für die Gebührenberechnung / Fee calculation sheet / Feuille de calcul des taxes — 1
- ☒ Abbuchungsauftrag / Debit order / Ordre de débit — Währung/Currency/Monnaie Betrag/Amount/Montant: eur 2552.00
- ☐ Scheck / Cheque / Chèque — Ausfüllung freigestellt / Optional / facultatif
- ☐ Sonstige Unterlagen (einzeln aufführen) / Other documents (specify) / Autres documents (préciser)

B. Beigefügte Dokumente / Accompanying documents / Eléments joints

- ☐ Gesonderte unterzeichnete Vollmacht / Separate signed power of attorney / Pouvoir distinct signé —

Die genannten Unterlagen sind am oben genannten Tag eingegangen. Die in der Kontrolliste (Feld VIII) des PCT-Antragformulars RO/101 angegebenen Blattzahlen wurden bei Eingang nicht geprüft. Die Anmeldung hat ebenfalls oben angeführte Anmeldenummer erhalten / The said items were received on the date indicated above. No check was made on receipt that the number of sheets indicated in the check list (box VIII) of the PCT Request Form RO/101 were correct. The application has been assigned the above-indicated application number / Les documents mentionnés ont été reçus à la date indiquée. L'exactitude du nombre de feuilles indiqué au bordereau (cadre VIII) du formulaire de requête PCT RO/101 n'a pas été contrôlée lors du dépot. Le numéro figurant ci-dessus a été attribué à la demande de brevet.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum))* *H100208WO / brä*

Box No. I TITLE OF INVENTION

Process for the Preparation of Geminal Difluoroalkanes

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Honeywell Specialty Chemicals Seelze GmbH
Wunstorfer Straße 40

30926 Seelze
DE

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SCHMAND, Horst Ludwig Karl
Kramerstr. 3

31542 Bad Nenndorf
DE

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DE

State *(that is, country)* of residence: DE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BUBLAK, Wolfgang
Bardehle Pagenberg Dost Altenburg Geissler

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Telephone No.
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Facsimile No.
089-92805-444

Teleprinter No.

Agent's registration No. with the Office:

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☒ **DE** Germany **is not designated** for any kind of national protection

☐ **KR** Republic of Korea **is not designated** for any kind of national protection

☐ **RU** Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 07/08/2003 07 August 2003	10336274.6	Germany		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / *EP*

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office))*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐	Box No.VIII (i)	Declaration as to the identity of the inventor
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent
☐	Box No.VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains:**

(a) the following number of **sheets in paper form:**

request (including declaration sheets) :	3
description (excluding sequence listing and/or tables related thereto) :	8
claims :	3
abstract :	1
drawings :	
Sub-total number of sheets :	15
sequence listing :	
tables related thereto :	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)	
Total number of sheets :	15

(b) ☐ **only in computer readable form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing:
- ☐ tables related thereto:

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*: — Number of items

1. ☒ fee calculation sheet : 1
2. ☐ original separate power of attorney :
3. ☐ original general power of attorney :
4. ☐ copy of general power of attorney; reference number, if any: :
5. ☐ statement explaining lack of signature :
6. ☐ priority document(s) identified in Box No. VI as item(s): :
7. ☐ translation of international application into *(language)*: :
8. ☐ separate indications concerning deposited microorganism or other biological material : :
9. ☐ sequence listing in computer readable form *(indicate type and number of carriers)*
   - (i) ☐ copy submitted for the purposes of international search under Rule 13*ter only* (and not as part of the international applicaton) :
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   - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column : :
10. ☐ tables in computer readable form related to sequence listing *(indicate type and number of carriers)*
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    - (ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*) :
    - (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :
11. ☐ other *(specify)* :

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Munich, May 27, 2004 / brä

Dr. Wolfgang Bublak, European Patent Attorney

For receiving Office use only

1. Date of actual receipt of the purported international application:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:
- ☐ received:
- ☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

H100208 BUW/brä

Process for the Preparation of Geminal Difluoroalkanes

The present invention relates to a process for the preparation of geminal difluoroalkanes, as well as to new compounds prepared by said process and their use as an intermediate of pharmaceutical products.

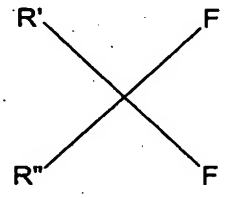
Owing to their advantageous biochemical properties geminal difluoroalkanes are of special significance, which is due to the fact that the CF_2-group is isopolar and isometric in relation to the ether oxygen and a R-CHOH group. According to conventional manufacturing processes, a corresponding ketone is converted to a geminal difluoroalkane using fluorophosgene (J. Am. Chem. Soc. 84 (1962) 4275), sulfur tetrafluoride (Org. Reactions 21 (1974) 1), DAST (Et_2NSF_3, J. Org. Chem. 40 (1975) 574) or trifluoroacetic acid anhydride or pyridine·HF (JP-A-63-054 332). Moreover, derivatized ketones such as hydrazones (J. Am. Chem. Soc. 109 (1987) 896), diazo compounds (J. Chem. Soc., Perkin Trans. 1 (1978) 1224) and thioketals (J. Org. Chem. 51 (1986) 3508) can be converted to geminal difluoroalkanes, respectively, using fluorine or halogen fluorides. In the present processes mainly gaseous and highly aggressive reagents are used that were generated using F_2 which involves a costly realisation of the conversion.

Recent literature has suggested to convert an unsubstituted oxime using a mixture of anhydrous hydrogen fluoride in ether in the presence of N_2O_4 (J. Fluorine Chem. 70 (1995) 207). However, the yield of this process is small. Concurrently, the conversion of an oxime using hydrogen fluoride in pyridine and nitrosyl tetrafluoroborate ($NOBF_4$) was published (Synlett (1994) 425). However, the reagent $NOBF_4$ is costly and ill- suited for the use in the industry. Furthermore, according to the above manufacturing processes, only unsubstituted oximes can be converted to the corresponding geminal difluoroalkanes.

Thus, it is the object of the present invention to overcome the above disadvantages of the prior art and to provide a process for the preparation of geminal difluoroalkanes which is specific, has sufficient yields, utilizes cost-effective reagents and which can also preferably be used for substituted difluoroalkanes.

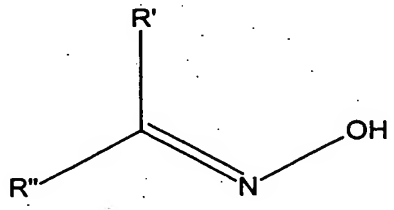
This object can be achieved by reacting an oxime with a nitrite and a complex consisting of hydrogen fluoride and an organic base.

Thus, the invention relates to a process for the preparation of a geminal difluoroalkane having the general formula (I),



(I)

wherein, independently from each other, R' and R" represent substituted alkyl-, aryl- or aralkyl or may be combined to form a cyclic system, characterized in that an oxime of the general formula (II)



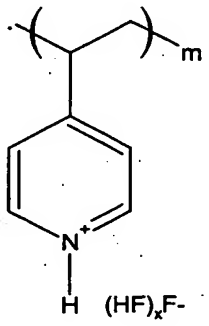
(II)

whereas R' and R" are defined as aforesaid, is converted using a nitrite and a complex comprising hydrogen fluoride and an organic base.

The oxime of the formula (II) is not particularly limited: in principle, any alkyl-, aryl- or aralkyl oxime can be used. If the oxime contains functional groups, these groups should be sufficiently stable with regard to acids and oxidants or be protected from fluorination accordingly. The oxime can be manufactured from the respective ketones by use of conventional processes. Thereby, 4-cyclohexanoneoxime carboxylic acid (esters) are parent compounds for particularly preferred difluoroalkanes according to the invention and novel, making them suitable for the use as intermediate compounds.

As the fluorination agent a combination of an hydrogen fluoride and an organic base may be used. Bases may be electron pair donors (Lewis bases) such as amines or ethers. In combination with an excess of hydrogen fluoride these organic bases containing free electron pairs form remarkably stable complexes of the general formula $BH^+(HF)_xF^-$, generally known as onium poly(hydrogen fluoride). Examples thereof are:

$R_2OH^+(HF)_xF^-$ (oxonium poly(hydrogen fluoride)), $C_5H_5NH^+(HF)_xF$ (pyridinium poly(hydrogen fluoride)), $R_3PH^+(HF)_xF^-$ (phosphonium poly(hydrogen fluoride)), $R_3NH^+(HF)_xF^-$ (ammonium poly(hydrogen fluoride)) and



(polyvinylpyridinium polyhydrogen fluoride).

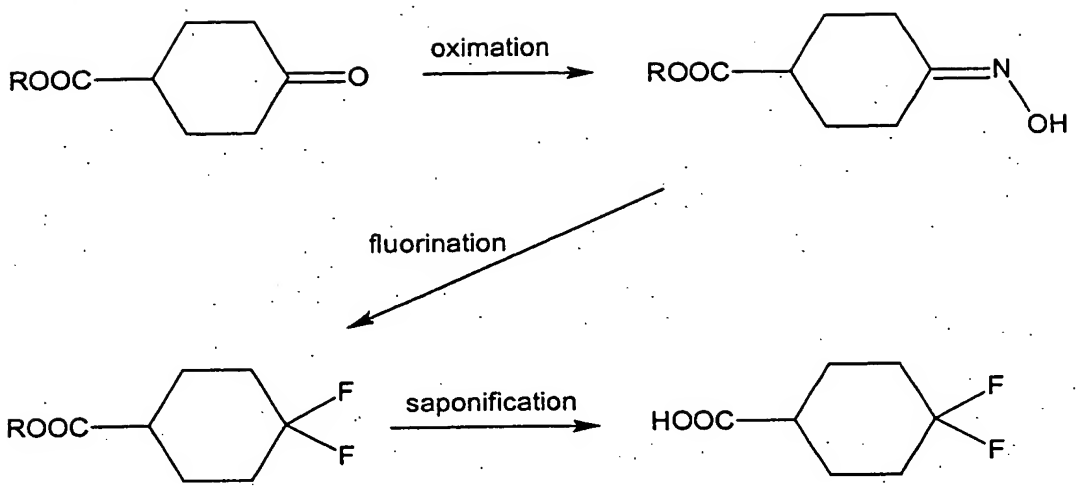
As the nitrite inorganic or organic nitrites, or a combination thereof can be used, however, for practical reasons, the use of sodium nitrite and/or potassium nitrite is preferred. If organic nitrites are used, pentylnitrite and butylnitrite are suitable candidates.

Preferably, the nitrite is added as a solid to the reaction mixture consisting of an oxime and onium poly(hydrogen fluoride). The reaction is highly exotermic and is carried out preferably at a temperature of about 0 °C. After conversion, the reaction mixture is further processed with water, as usual.

The starting materials and the reagents can be added in any order.

In order to provide the hydrogen fluoride with the necessary reactivity, the presence of an organic base is preferred. If nitrosyl tetrafluoroborate is used as a fluorination agent, this results in small yields, particularly for substituted oximes as shown in Comparative Example 1 below. Converting an oxime using only anhydrous HF and nitrite results in a very small yield as shown in a Comparative Example 2 below.

The reaction scheme for the production of the preferred compound 4,4-difluorocyclohexane-carboxylic acid can be shown as follows.



The following examples illustrate the above discussion.

Example 1

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester (method A)

In a nitrogen deactivated 250 ml PFA-flask comprising a magnetic stirrer, a thermoindicator, an N_2-inlet, a dosing pipe with a single-use syringe, a bubble gauge and an exhaust tube, 100 g pyridine/HF with wt. 70% HF were added and cooled down to 0 °C. While stirring for 20 minutes, 6 g sodium nitrite were added in small portions. After continued stirring for another 10 minutes at 0 °C 8.6 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were added via a dosing pipe with a single-use syringe over a period of 55 minutes. Thereby, the temperature was kept constant in a range between -2 and 1.5 °C. Near completion of the dosing, gas was generated. The reaction mixture was then stirred for another 2 hours at 0 °C.

300 g ice were put in a 2l PE beaker, and the reaction mixture was poured in at constant stirring. The mixture was then extracted using 350 ml fluobenzene. Water was added to the combined organic phases, followed by neutralizing them with a saturated sodium hydrogen carbonate solution. After phase separation, the or-

ganic lower phase was washed with water, filtered and narrowed down. 5.77 g of the title compound were obtained (yield 64.7%), which was measured using gas chromatography.

Example 2

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester (method B)

In a nitrogen deactivated 250 ml PFA-flask comprising a magnetic stirrer, a thermoindicator, an N_2-inlet, a dosing pipe with a single-use syringe, a bubble gauge and an exhaust tube, 100 g pyridine/HF with wt. 70% HF were added and cooled down to 0 °C. Then, 27.8 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were added via a dosing pipe with a single-use syringe over a period of 20 minutes after continued stirring for another 30 minutes at 0 °C. 12.4 g sodium nitrite were added in small portions. Thereby, the temperature was kept constant in a range between -2 and 1.5 °C. Near completion of the dosing gas was generated. The reaction mixture was then stirred for another 2 hours at 0 °C.

300 g ice were put in a 2l PE beaker, and the reaction mixture was poured in at constant stirring. The mixture was then extracted using 350 ml fluobenzene. Water was added to the combined organic phases, followed by neutralizing them with a saturated sodium hydrogen carbonate solution. After phase separation, the organic lower phase was washed with water, filtered and narrowed down. 18.2 g of the title compound were obtained (yield 63.0%), which was measured using gas chromatography.

Example 3

Preparation of 4-cyclohexanoneoxime-carboxylic acid ethyl ester

In a 500 ml three necked-flask comprising an stirrer, a cooler, a thermometer and a drip funnel, 200 ml water, 81.6 g sodium acetate and 52.2 g hydroxylamine hy-

drochloride were added and heated up to 60 °C. Then, 85.2 g 4-cyclohexanone-carboxylic acid ethyl ester were added to the mixture over a period of 1 hour. The emulsion was stirred for 1.5 hours and left to stand over night at room temperature. This was followed by adding 50 ml tert-butyl methyl ether, by shaking, by separating the lower phase and by a repeated extraction of 50 ml tert-butyl methyl ether. Then, the combined organic phases were washed several times with water, filtered, dried and narrowed down under reduced pressure. 86.8 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were obtained (yield 93.6%).

Comparative Example 1

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester using $NOBF_4$

In a 200 ml PFA-flask with N_2-inlet, thermoindicator, dosing pipe with syringe, cooler, receiving flask, bubble gauge and exhaust tube, 100 g of pryidine/HF with 70 wt% HF were added and cooled down to 0 °C. Subsequently, 6.6 g nitrosyl tetrafluoroborate (white coarse crystals) were slowly added. 8.6 g of 4-cyclohexanone oxime carboxylic acid ethyl ester were drawn into a 10 ml syringe and added at -7 to -2 °C within 1 hour via the pipe. Then, the reaction mixture was heated up to room temperature and stirred for another 4 hours at room temperature. After about 1 hour the temperature rose to 27 °C, gas was bubbling up and N_2O could be observed in the bubble gauge. This was followed by cooling down with an ice bath. After the usual procedures, 3.4 g of the title compound (yield: 38.5%) could be isolated.

Comparative Example 2

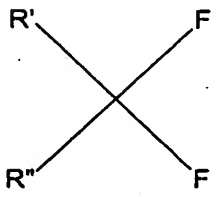
Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester using HF without an organic base

70 g of HF were put into a 250 ml PFA- round bottom flask which was cooled in an ice/sodium chloride-freezing mixture. At a temperature of about -10 °C 18.5 g of 4-cyclohexanone oxime carboxylic acid ethyl ester were added to the HF, followed by portionwise adding 7 g $NaNO_2$ to the solution within 2 hours. In the meantime, the flask was closed with a bubble gauge which was removed during the addition of the nitrite. Only a minor gas generation could be observed. The reaction temperature was limited to a range between -5 °C and 2 °C. After dosing the nitrite, the reaction mixture was poured on ice, and after phase separation a sample was taken from the organic phase.

The GC-analysis showed 84 area% starting material, 7.6 area% of 4,4- difluoro-cyclohexane-carboxylic acid ester and 5.6 area% of a monofluoro-compound. The assignment was performed using GC/MS.

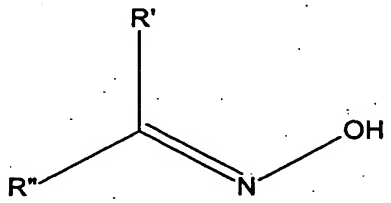
Claims

1. Process for the preparation of a geminal difluoroalkane of the general formula (I),



(I)

wherein, independently from each other, R' and R" represent substituted alkyl-, aryl- or aralkyl or may be combined by the formation of a cyclic system, characterized in that an oxime of the general formula (II)



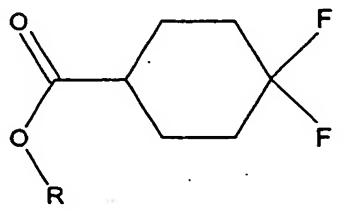
(II)

whereas R' and R" are defined as aforesaid, is converted using a nitrite and a complex consisting of hydrogen fluoride and an organic base.

2. Process according to claim 1, characterized in that R' and R" represent C_1 - C_8-alkyl or aryl or, in combination with the carbon atom they are bound to, C_3 - C_8-alkyl.

3. Process according to claim 2, characterized in that R' and R" form a cyclohexane ring in combination with the carbon atom they are bound to.

4. Process according to claim 3, characterized in that the difluoroalkane of the general formula (I) is a difluorocyclohexane-carboxylic acid ester of the general formula (I'),



(I')

wherein R represents a hydrogen atom or C_1 - C_8-alkyl.

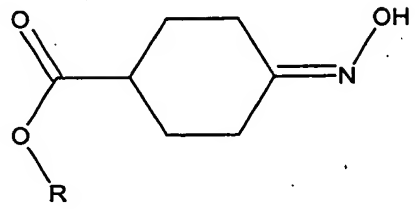
5. Process according to claim 4, characterized in that the difluoroalkane of the general formula (I') is 4,4-difluorocyclohexane-carboxylic acid ethyl ester.

6. Process according to claim 4, characterized in that the difluoroalkane is 4,4-difluorocyclohexane-carboxylic acid.

7. Difluorocyclohexane-carboxylic acid ester of the general formula (I') according to claim 4, wherein R represents a hydrogen atom or a C_1 - C_8-alkyl residue.

8. Compound according to claim 7, namely 4,4-difluorocyclohexane-carboxylic acid.

9. Compound according to the general formula (II')



(II')

wherein R represents a hydrogen atom or a C_1 - C_8-alkyl residue.

10. Use of 4,4-difluorocyclohexane-carboxylic acid as an intermediate in the manufacture of pharmaceutical products.

Abstract

The invention relates to a process for the preparation of a substituted or unsubstituted geminal difluoroalkane, wherein an oxime is converted to the geminal difluoroalkane using a nitrite and a complex consisting of HF and an organic base, as well as its use as an intermediate in the manufacture of pharmaceutical products.